Randomized Clinical Trials of Neuroprotective Agents in Parkinson's Disease: The NINDS Registry

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Introduction

No drug has been shown convincingly to slow the progression of Parkinson's disease. Efficacious neuroprotective agents (i.e. disease-modifying drugs) could importantly impact neurological disability for hundreds of thousands of Americans with this disorder. The design of future randomized clinical trials of neuroprotective drugs optimally should be planned with awareness of the previous trials undertaken with the same goal, to profit from their experience. Here, all randomized clinical trials in humans testing putative neuroprotective drugs in Parkinson's disease are identified that have been previously published or about which information is publicly available, and their key design features summarized.

Additional information about ongoing trials and corrections are welcome and will be incorporated into regular updates of this document.

Methods

Randomized trials testing agents to slow the progression of Parkinson's disease were identified by computerized search of the OVID/MEDLINE databases from 1966 through April 2003, not restricted by language, using the key words of Parkinson's disease, clinical trial, neuroprotection/neuroprotective. Citations in major recent review articles

about neuroprotection in Parkinson's disease were additionally reviewed, and inquiries were made to experts working in the field. Pilot trials and trials published to date in abstract were included. Trials were restricted to those with pre-specified clinical, functional imaging, or autopsy criteria for evidence of neuroprotection (i.e. those with post hoc analysis evaluating putative neuroprotective effects were not included); surgical trials, trials requiring intraventricular administration, and trials testing deep brain stimulation were not considered. Clinical trials that were excluded, but that are occasionally cited in the literature as neuroprotection trials, are listed in the last section a long with the reason for their exclusion.

Regarding ongoing trials sponsored by pharmaceutical companies, the Pharmaceutical Research and Manufacturers of America website (http://www.phrma.org/newmedicines/newmedsdb/drugs.cfm) was surveyed, and the companies contacted regarding providing information for this survey. Several declined or did not respond. Consequently, while we have anecdotal knowledge of ongoing trials sponsored by pharmaceutical companies, they are not included here unless specific information was supplied by the sponsor or if there are other sources of publicly accessible information.

Results

Fourteen completed randomized clinical trials aimed at assessment of potential neuroprotective agents were identified (Table). Of 3652 total participants, about 40% (n=1512) were involved in six trials testing monoamine oxidase-B inhibitors (selegiline or lazabemide). The primary outcome in earlier trials was typically the need to initiate levodopa therapy (analyzed as either the mean time to initiation or frequency of participants requiring levodopa during a pre-specified follow-up interval) in levodopa-naïve patients. Later trials most often used the total UPDRS score or subscale scores, which could be monitored following a washout phase of variable duration in order to assess the contribution of occult symptomatic effects. Recently, neuroimaging

biomarkers using PET or SPECT imaging have been used as primary or secondary outcomes. At present, there is a general consensus that the correlation between functional neuroimaging outcome and clinical disease status has not been adequately established to permit the use of functional imaging as a surrogate marker for establishing clinical neuroprotection (*Mov Disord* 2002; 17: 229-232; *Ann Neurol* 2003; 53(Suppl 3): S87-99).

Since DATATOP initiated recruitment in 1987, there have been an estimated 1,450,000 Americans with Parkinson's disease (700,000 prevalent cases in 1987 and 50,000 incident cases yearly since then). Considering American patients with Parkinson's disease participating in the clinical trials testing neuroprotective agents (estimated to be about 2700), only about 0.2% (or about 1 in 500) of Americans with Parkinson's disease have participated in these clinical trials. Considering incident cases potentially eligible for trials of newly-diagnosed PD patients, only about 0.4% (or about 1 in 250) of Americans with Parkinson's disease have participated in clinical trials.

Table. Randomized Trials Testing Neuroprotective Agents in Parkinson's Disease*

Trial	Active Agents	N	Primary Outcome
Completed Trials			
1. DATATOP (1989)**	selegiline & tocopherol	800	Need for l-dopa
2. Tetrud and Langston (1989)	selegiline	54	Need for l-dopa
3. SINDEPAR (1995)	selegiline	101	UPDRS
4. ROADS (1996)	lazabemide	321	Need for l-dopa
5. Swedish Selegiline (1998)	selegiline	157	Need for l-dopa
6. OPC-14117 (1998)**	OPC-14117	28	Not available
7. Norwegian-Danish (1999)	selegiline	79	UPDRS
8. NIL-A (2001)	neuroimmunophilin A	300	UPDRS motor
9. QE-2 (2002)**	coenzyme Q10	80	UPDRS
10. CALM-PD (2002)	pramipexole vs. l-dopa	82	beta-CIT SPECT
11. REAL-PET (2003)	ropinirole vs. l-dopa	186	fluoro-dopa PET
12. Jankovic and Hunter (2002)	riluzole	20	UPDRS
13. ELLDOPA (2002)**	l-dopa	360	UPDRS
14. Riluzole (2003)	riluzole	1084	Need for sympt Rx
Ongoing Trials			
15. NINDS NET PD (2003-5)** (series of pilot trials)	minocycline, creatine, CoQ10, GPI-1485	390	UPDRS

*Listed in order of the year of the major available publication; sympt Rx = symptomatic treatment with levodopa or dopamine agonists; UPDRS = Unified Parkinson Disease Rating Scale; PET = Positron emission tomography; SPECT = single photon emission computed tomography, sympt Rx = symptomatic therapy.
** Sponsored by NINDS (five trials involving 1658 particpants)

Description of Individual Trials
(listed alphabetically by study name or principal investigator)

CALM-PD
Investigators: K Marek, Parkinson Study Group.
Sponsor: Pharmacia and Boehringer Ingelheim.
Time period: 1996-2001.
Design: randomized, double-blinded, multi-center.
Interventions: pramipexole 0.5mg/d vs. l-dopa/carbidopa 25/100 t.i.d. initial dosage.
Primary outcome: change in [123I] beta-CIT SPECT uptake after 46 months; secondary outcome was UPDRS in the "defined off" state.
Eligibility: Subgroup of CALM-PD participants at selected sites; early Parkinson's disease.
Number of participants: 82.
Follow-up duration: 46 months.
Efficacy results: 40% reduction in loss of beta-CIT uptake in those assigned pramipexole vs. l-dopa (p=0.01).
Main publications: *JAMA* 2002; 287; 1653-61; *JAMA* 2000; 284: 1931-8; *Neurology* 2003; 60 (Suppl 1): A293 (abstract).
Comments/Limitations: The authors conclude: "these imaging data strongly suggest that treatment with pramipexole may slow and/or levodopa may accelerate the rate of loss of nigrostriatal dopamine neurons…" *Neurology* 2002; 58 (Suppl 3): A82 (abstract). However, there is uncertainty about the interpretationof the imaging data and the observed effects may be due to pharmacological effects of pramipexole on the dopamine transporter. Additional follow-up after 12 months of unrestricted treatment with PD medications in 56 participants continued to reduced loss in striatal uptake in those initially assigned pramipexole.

DATATOP
Investigators: I Shoulson, Parkinson Study Group.
Sponsor: NINDS/NIH.
Time period: 1987-1989.
Design: randomized, double-blinded, two by two factorial, multicenter.
Interventions: selegiline 10mg/d and alpha-tocopherol 2000 iu/d vs. placebo.
Primary outcome: need for levodopa therapy as perceived by study physician.
Eligibility: early, levodopa naïve.
Number of participants: 800.
Follow-up duration: about 12 months for selegiline and about 14 months for tocopherol.
Efficacy results:
- selegiline: inconclusive due to confounding by unanticipated symptomatic effects.
- tocopherol: negative.

Main publications: *NEJM* 1993; 328: 176-83, *Ann Neurol* 1996; 39: 29-36, *Ann Neurol* 2002; 51: 604-12.
Comments/Limitations: Terminated at second interim analysis due to apparent benefit of selegiline. An unexpected symptomatic benefit of selegiline did not permit

neuroprotection to be convincingly assessed despite salvage efforts during additional follow-up: "no firm evidence that deprenyl [seligiline] exerts neuroprotective effects."

ELLDOPA
Investigators: S Fahn, Parkinson Study Group.
Sponsor: NINDS/NIH.
Time period: 1998-2001.
Design: multi-center, double-blinded, randomized trial.
Interventions: levodopa (3 dosages) and placebo (4 cells).
Primary outcome: change in UPDRS score after a 14-day wash-out.
Eligibility: early (<2 yrs from diagnosis), levodopa naïve.
Number of participants: 360.
Follow-up duration: about 9 months.
Efficacy results: pending.
Main publication: *Arch Neurol* 1999; 56: 529-35 (design summary); results reported orally late 2002, nothing yet in print.
Comments/Limitations: The primary objective is to assess "whether l-dopa slows or hastens the progression of Parkinson's disease." The two-week washout period for assessment of neuroprotective effects is relatively brief.

Jankovic & Hunter
Investigators: J Jankovic, C Hunter
Sponsor: Aventis Pharmaceuticals.
Time period: late 1990's-2000.
Design: randomized, double-blinded, single center, pilot trial.
Interventions: riluzole 100mg/d vs. placebo.
Primary outcome: UPDRS.
Eligibility: early Parkinson's, levodopa naïve.
Number of participants: 20.
Follow-up duration: 6 months.
Efficacy results: no significant difference; riluzole well-tolerated.
Main publication: *Parkinsonism and Related Disorders* 2002; 8: 271-6.
Comments/Limitations: Pilot study with very low power for detection of efficacy.

NIL-A
Investigators: unknown.
Sponsor: Amgen and Gilford Pharmaceuticals
Time period: 2000-2001.
Design: multi-center phase II, double-blinded, randomized.
Interventions: neuroimmunophilin A/ GPI 1485 (two dosages, 200 qid or 1000mg qid) vs. placebo.
Primary outcome: UPDRS motor score; secondary outcome beta-CIT SPECT.
Eligibility: Early-to-moderate PD.
Number of participants: 300.
Follow-up duration: 6 months.

Efficacy results: "Trends…not significant" on UPDRS motor scores after 6 months of follow-up; p=0.03 difference in Hoehn/Yahr scores; beta-CIT SPECT in a subgroup of 105 participants showed promising trends.
Main publication: press release from Amgen in July 26, 2001 is the only published source: www.corporate-ir.net/ireye/ir_site.zhtml?ticker=GLFD&script=410&layout=-6&item_id195083
Comments/Limitations: Results discussed in Gold BG, Nutt JG in *Curr Opinion in Pharmacology* 2002; 2: 82-6.: The trial was designed and powered to detect only very robust treatment effects. "It would be unfortunate, in view of the neuroprotective and restorative potential of this class of compounds, if the NIL-A trial failure leads to the abandonment of this very promising area." No peer-reviewed results published to date.

NINDS NET PD
Investigators: NET-PD Investigators
Sponsor: NINDS/NIH.
Time period: 2003-2005.
Design: multi-center, double-blinded, randomized trials.
Interventions: minocycline, creatine, coenzyme Q10, neuroimmunophilin A (GPI-1485) vs. placebo.
Primary outcome: change in UPDRS.
Eligibility: within 5 years of diagnosis and not receiving symptomatic treatment.
Number of participants: 390 divided between four active treatments and placebo.
Follow-up duration: 12-18 months.
Efficacy results: pending.
Main publication: none (ongoing trials).
Comments/Limitations: These are pilot trials designed to assess whether these agents warrant further study in phase III comparative efficacy trials. For more information, contact Dr. Bernard Ravina, NINDS project officer (ravinab@ninds.nih.gov).

Norwegian-Danish Study
Investigators: JP Larsen and the Norwegian-Danish Study Group.
Sponsor: Orion Pharma and Ercopharm.
Time period: 1989-1997.
Design: randomized, double-blinded, multi-center.
Intervention: selegiline 10mg/d vs. placebo; all received l-dopa.
Primary outcome: UPDRS score after one month wash-out.
Eligibility: early PD treated with l-dopa for 6 months or less.
Number of participants: 79.
Follow-up duration: 60 months.
Efficacy results: $p<0.01$ for differences in UPDRS after one month washout of selegiline/placebo.
Main publication: *European J Neurol* 1999; 6: 539-47.
Comments/Limitations: Several design features make results difficult to interpret. While 163 patients were randomized, assessment of neuroprotective effects was based on analysis of an ill-described subgroup of 79 participants who completed five years of treatment and who underwent the one month washout. Higher dosages of l-dopa were

required in the placebo group than in the selegiline group to control symptoms during the course of the trial; l-dopa "neurotoxicity" is an alternative explanation for the results. No decline in UPDRS was seen during the one month washout phase (i.e. selegiline had no measurable symptomatic effect after five years of treatment), conflicting with other trials (albeit shorter treatment durations). The authors conclude: "The results cannot be easily explained by a symptomatic effect of selegiline."

OPC-14117
Investigators: TN Chase.
Sponsor: Experimental Therapeutics Branch/NINDS.
Time period: 1995-1998.
Design: phase II randomized trial, intramural NINDS
Interventions: OPC-14117 (lipophilic free radical scavenger) vs. placebo
Primary outcome: not known.
Eligibility: not known.
Number of participants: 28.
Follow-up duration: up to five years (terminated early).
Efficacy results: not known.
Main publication: unpublished.
Comments/Limitations: No published information about this trial. Apparently terminated before completion when Otsuka Pharmaceuticals ceased manufacture of the drug.

QE2
Investigators: C Shults et al.
Sponsor: NINDS/NIH.
Time period: 1998-2001.
Design: randomized, double-blinded, pilot trial, multi-center.
Intervention: coenzyme Q10 (ubiquinone) – 3 dosages: 300mg/d, 600mg/d, 1200mg/d vs. placebo
Primary outcome: dosage-related trend in change in UPDRS score.
Eligibility: no antiParkinsonian medications.
Number of participants: 80 (20 in each treatment group).
Follow-up duration: 16 months.
Efficacy results: positive trend (p=0.09) in dosage-related decrease in UPDRS.
Main publication: *Arch Neurol* 2002 ;59:1541-50
Comments/Limitations: The authors conclude "Coenzyme Q10….appears to slow progressive deterioration of function in early PD." This pilot study was seeking a beneficial trend with increasing dosages vs. placebo. Only the 1200mg dose was significantly different from placebo at the p=0.05 level, without adjustment for multiple comparisons.

REAL-PET
Investigators: AL Whone et al.
Sponsor: GlaxoSmithKline.
Time period: about 2000.
Design: multi-center, double-blinded, randomized trial.

Interventions: ropinirole (mean dosage 12 mg/d) vs. l-dopa/carbidopa (mean dosage 559 mg/d).
Primary outcome: change in putaminal fluoro-dopa uptake by PET; secondary outcomes included the UPDRS motor score (on therapy) and Clinical Global Impression scale.
Eligibility: early l-dopa-naïve.
Number of participants: 186.
Duration of follow-up: 24 months.
Efficacy results: 34% reduction in loss of fluoro-dopa uptake by ropinirole vs. l-dopa (p=0.02) among 127 participants undergoing a two-year PET.
Main publication: *Ann Neurol* 2003; 54: 93-101.
Comments/Limitations: The authors conclude: "Ropinirole is associated with slower progression of PD than levodopa as assessed by fluoro-dopa PET…we cannot distinguish whether ropinirole was acting as a neuroprotectant and slowing the rate of dopamine terminal loss or L-dopa was increasing the rate of terminal loss (or a combination of both effects)… .it is not possible to tell whether the slower rate of terminal loss with ropinirole equates to long-term clinical benefit." PET assessment undertaken after a minimum of 12 hours after last dosing; longer washout for assessment of clinical outcomes was not undertaken.

Riluzole (Aventis)
Investigators: O Rascol, W Olanow, D Brooks, G Koch, P Truffinet, R Bejuit
Sponsor: Aventis Pharmaceuticals.
Time period: 1999-2001.
Design: randomized, double-blinded, multicenter.
Interventions: riluzole 100mg/d vs. riluzole 200mg/d vs. placebo.
Primary outcome: delay time to levodopa or dopamine agonist use (secondary outcomes: UPDRS after a 60-day washout at the end of the study; 18F-dopa PET imaging)
Eligibility: untreated PD patients.
Number of participants: 1084.
Follow-up duration: two-thirds of participants reached two-year follow-up.
Effiacy results: not specifically known (see comments, below).
Main publications: *Neurology* 2003; 60 (Suppl 1): A288. (abstract)
Comments/Limitations: Terminated at the second planned interim analysis due to futility. The probability of starting symptomatic therapies during the first 18 months was 0.69 on placebo and 0.71 on riluzole. There was no difference on secondary endpoints. "There was no indication that riluzole at the dose of 100mg/d and 200mg/d slowed the progression of PD nor exhibited symptomatic antiparkinsonian activity."

ROADS
Investigators: K Kieburtz, Parkinson Study Group
Sponsor/P.I.: Hoffman La Roche.
Time period: 1992-1994.
Design: randomized, double-blinded, multi-center.
Interventions: lazabemide 25mg. 50mg, 100mg and 200mg/d vs. placebo.
Primary outcome: need for levodopa therapy as perceived by the study physician.
Eligibility: early PD.

Number of participants: 321.
Follow-up duration: 12 months
Efficacy results: See comments/limitations, below.
Main publication: *Ann Neurol* 1996; 40: 99-107.
Comments/Limitations: While ostensibly "positive" results at all dosages, confounding by symptomatic effects similar to DATATOP: "limitations of clinical trial design precluded our ability to define….whether or not lazabemide slow the underlying progression of disease."

SINDEPAR
Investigators: CW Olanow et al.
Sponsors: National Parkinson's Foundation, Sandoz, Somerset.
Time period: early 1990s.
Design: randomized, double-blinded, two centers.
Interventions: selegiline 10mg/d vs. placebo, also randomized to levodopa and bromocryptine in a two by two factorial design.
Primary outcome: total UPDRS score after a 60 day wash-out of seligiline and 7-day washout of levodopa or bromocryptine (a subgroup of 23 patients underwent a 14-day washout).
Eligibility: early, untreated Parkinson patients.
Number of participants: 101.
Follow-up duration: 12 months.
Efficacy results: Placebo patients deteriorated by 5.8pts vs. selegiline-assigned patients by 0.4 pts on UPDRS ($p<.001$).
Main publication: *Ann Neurol* 1995; 38: 771-9.
Comments/Limitations: "These findings are not readily explained by the drug's symptomatic effects and are consistent with the hypothesis that [selegiline] has a neuroprotective effect." "However…some doubt remains because it is not clear that washout was sufficient…."(*Ann Neurol* 2003; 53 (Suppl 3): S89).

Swedish Selegiline Study
Investigators: S Palhagen, Swedish Parkinson Study Group
Sponsor: not stated.
Time period: early 1990s.
Design: randomized, double-blinded, multicenter..
Interventions: selegiline 10mg/d vs. placebo.
Primary outcome: need for levodopa therapy.
Eligibility: early PD, levodopa naïve.
Number of participants: 157.
Follow-up duration: mean about one year, many up to three years.
Efficacy results: Favored selegiline with persistent difference in disability after 8 wk washout.
Main publication: *Neurology* 1998; 51: 520-5.
Comments/Limitations: "supporting the concept of neuroprotective properties of the drug." The washout period may not have been sufficient.

Tetrud & Langston
Investigators: JW Tetrud, JW Langston.
Sponsor: California Parkinson's Foundation
Time period: mid-1980s.
Design: randomized, double-blinded, single center.
Interventions: selegiline 10mg/d vs. placebo.
Primary outcome: time to levodopa therapy.
Eligibility: early PD, levodopa naïve.
Number of participants: 54.
Follow-up duration: Not stated.
Efficacy results: Benefit of selegiline; no washout effect detected indicating symptomatic effects.
Main publication: *Science* 1989; 245: 519-22.
Comments/Limitations: the generally accepted short-term symptomatic effects of selegiline were not detected, possibly because of the relatively small sample size.

Excluded Clinical Trials
(alphabetically by eponym or principal investigator)

SELEDO (Przuntek H et al. *European J Neurol* 1999; 6: 141-150) is occasionally listed as a trial supporting the neuroprotective effects of selegiline. The primary outcome was the time to a 50% increase in l-dopa dose among the 120 participants with early Parkinson's disease who were randomized to receive either l-dopa monotherapy or l-dopa combined with selegiline. "The effect of selegiline was greater in the first year of treatment and this difference remained stable over the further course"; the investigators were cautious about attributing the observed benefits of combined treatment with selegiline to neuroprotective mechanisms. In contrast to this statement, the Kaplan-Meier plot of the primay study outcome (Figure 1 of the published report) shows continuing divergence well after one year of treatment that would not easily be accounted for by symptomatic effects. This trial is excluded from Table 1 because pre-specified criteria for putative neuroprotective effects was not part of its design.

TEMPO (Parkinson Study Group, *Arch Neurol* 2002; 59: 1937-43). The primary outcome was change in UPDRS between baseline and 26 weeks (i.e. symptomatic effects); no specific assessment of neuroprotective effects was included in the main results paper.